BI/CH 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic — Exam-1 material

Fermentations
Pyruvate
Krebs' Cycle
Oxidative Phosphorylation
- Electron transport
- Chemiosmotic theory: Phosphorylation

Exam-2 material

Fat Catabolism
Fatty acid Catabolism
- Mobilization from tissues (mostly adipose)
- Activation of fatty acids
- Transport; carnitine
- Oxidation: β-oxidation, 4 steps:

Protein Catabolism
Amino-Acid Degradation
- Dealing with the nitrogen; Urea Cycle
- Dealing with the carbon; Seven Families

Nucleic Acid & Nucleotide Degradation

Exam-3 material

PHOTOSYNTHESIS:

Overview of Photosynthesis
Key experiments:
Light Reactions
- energy in a photon
- pigments
- HOW
- Light absorbing complexes-"red-drop experiment"
  - Reaction center
  - Photosystems (PS)
    - PSII – oxygen from water splitting
    - PSI – NADPH

Proton Motive Force – ATP
Overview of light reactions

ANABOLISM I: Carbohydrates

Carbon Assimilation – Calvin Cycle
- Stage One – **Rubisco**
  - Carboxylase
  - Oxygenase
  - Glycolate cycle

  } Know mechanism
- Stage Two – making sugar
- Stage Three – remaking Ru 1,5P2

Overview and regulation
Calvin cycle connections to biosynthesis
C4 versus C3 plants
Kornberg cycle – glyoxylate

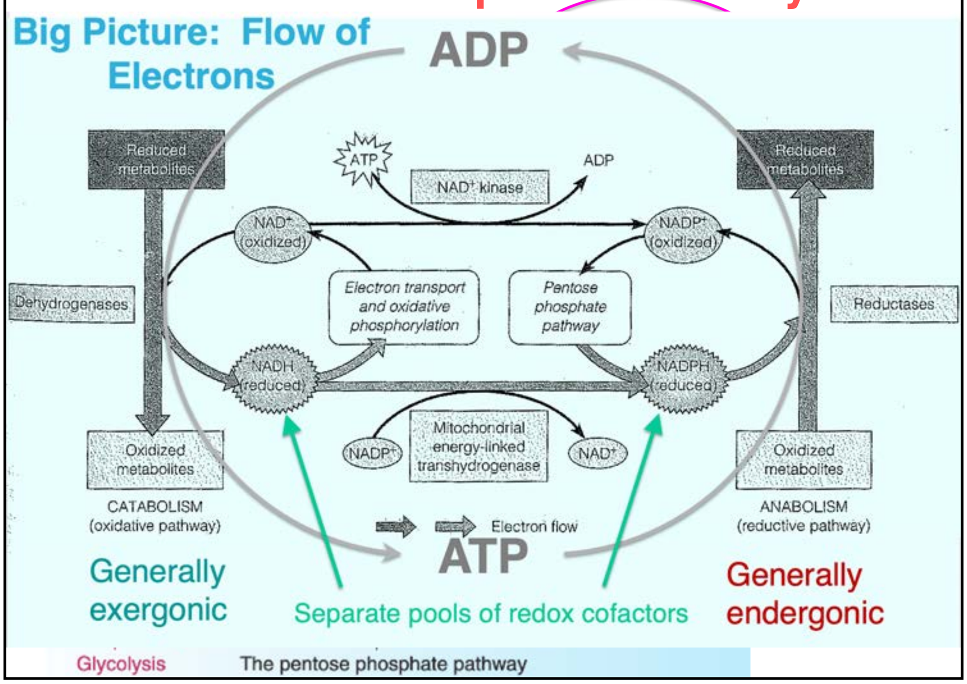
Carbohydrate Biosynthesis in Animals
- precursors
- Cori cycle

Gluconeogenesis
- reversible steps
- irreversible steps – four
  - energetics
  - 2-steps to PEP
    - mitochondria
    - Pyr carboxylase-biotin
    - PEPCK
  - FBPase
  - G6Pase

Glycogen Synthesis
- UDP-Glc
- Glycogen synthase
- branching

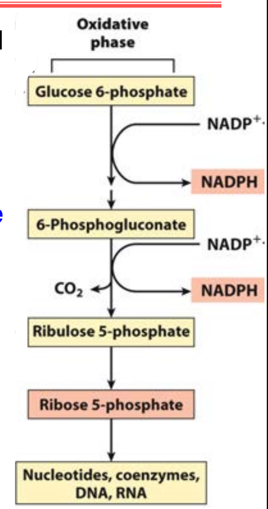
Pentose-Phosphate Pathway
Regulation of Carbohydrate Metabolism
Anaplerotic reactions

Pentose Phosphate Pathway



Pentose Phosphate Pathway

- Included in Anabolism because it provides the NADPH needed for so many biosynthetic reduction reactions, as well as the synthesis of pentoses.
- But, can also be used for a shunt in the **catabolism** of Glc 6-P.
- The main products are NADPH and ribose 5-phosphate (Rib 5-P).
- Oxidative Phase oxidizes Glc 6-P to make NADPH
- Non-oxidative Phase re-cycles pentoses to hexoses if not needed for biosynthesis.



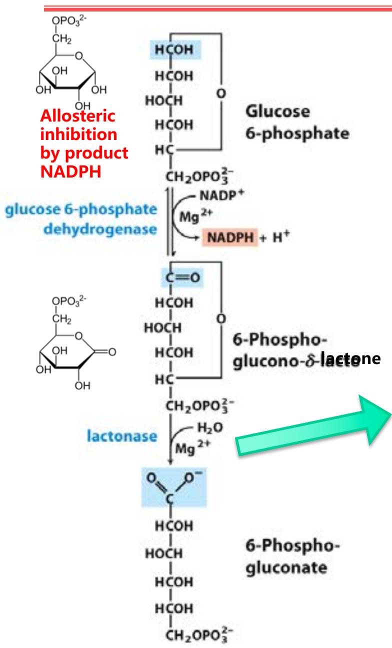
Uses of Pentose Phosphate Pathway (PPP):

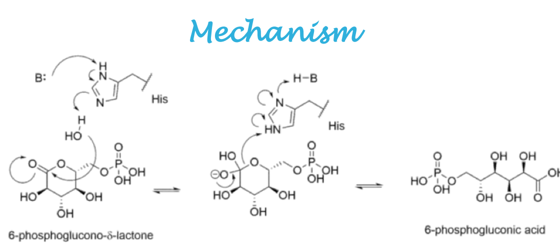
➢NADPH is an electron donor.
- reductive biosynthesis of fatty acids and steroids
- reductive biosynthesis of amino acids and nucleotide bases
- repair of oxidative damage

➢Ribose 5-phosphate is a biosynthetic precursor of nucleotides.
- used in DNA and RNA synthesis
- or synthesis of some coenzymes

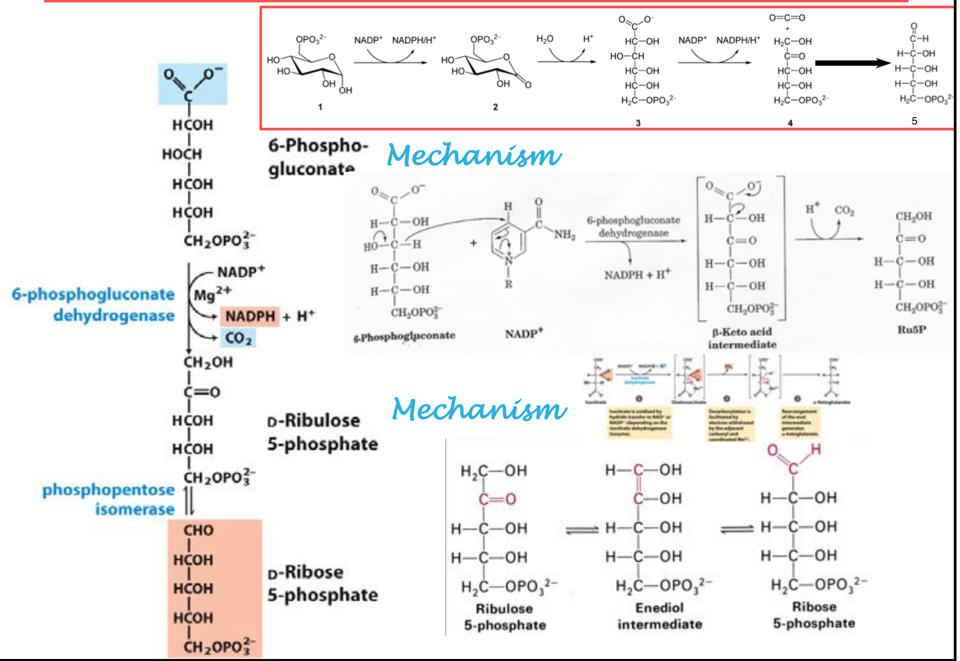
Pentose Phosphate Pathway

Oxidative Phase Generates NADPH and a Pentose

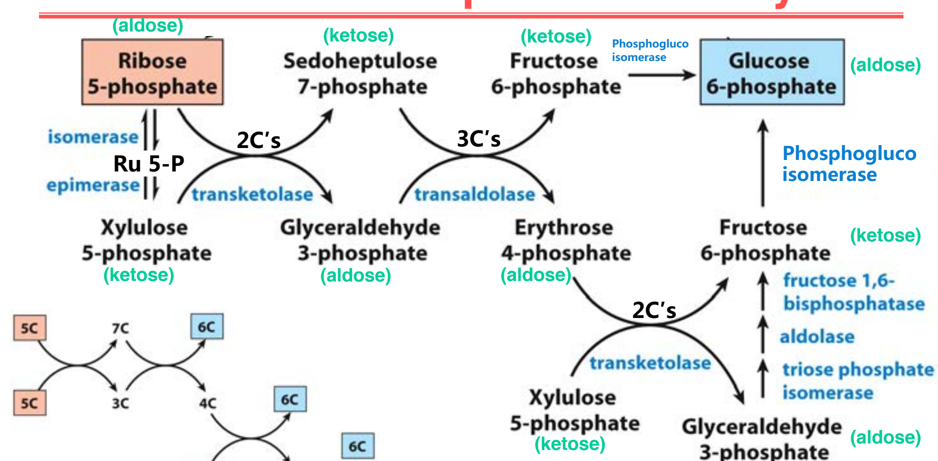


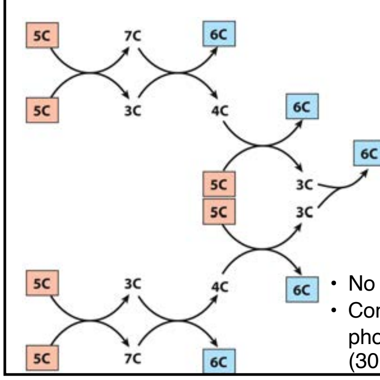


Pentose Phosphate Pathway



Pentose Phosphate Pathway

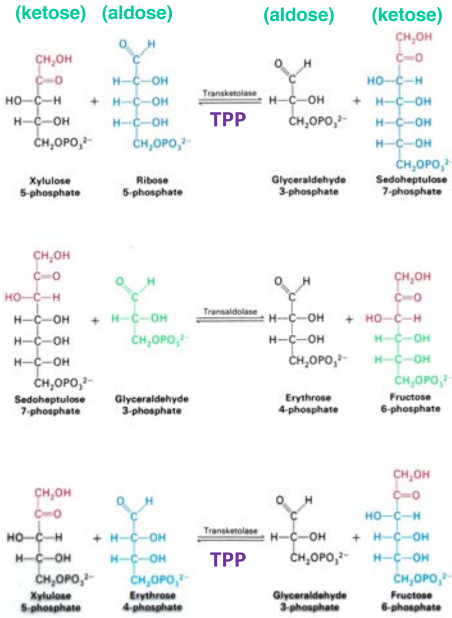


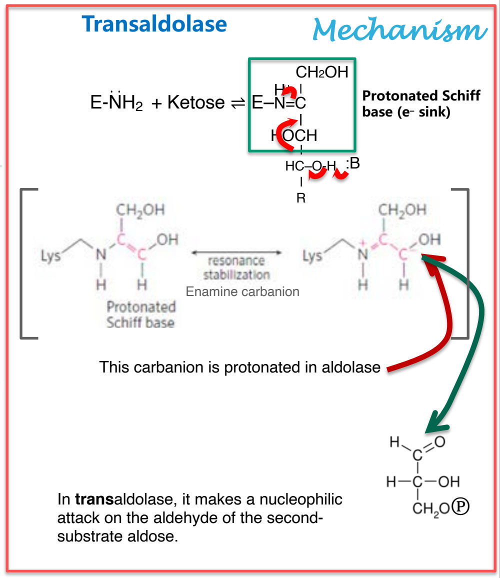


Non-oxidative Phase
Interconverts Rib 5-P to form Glc 6-P

- No ATP is used in the non-oxidative phase.
- Complete conversion of ribose-5-phosphate to glucose-6-phosphate requires 6 Rib 5-P (30 carbons) to make 5 Glc 6-P (30 carbons).

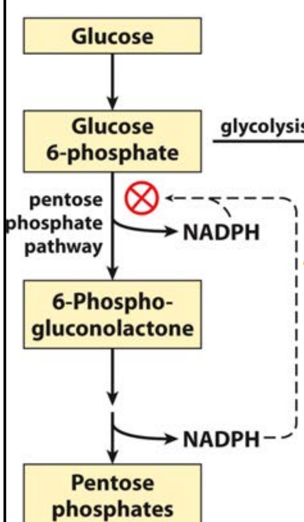
Pentose Phosphate Pathway

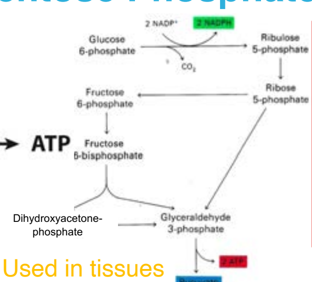


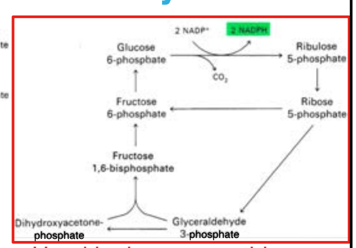


Pentose Phosphate Pathway

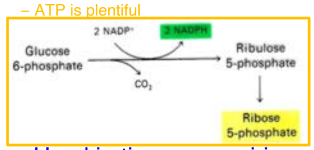
NADPH Regulates Partitioning into Glycolysis versus Pentose Phosphate Pathway

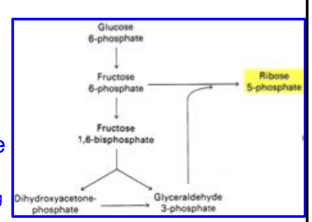






- Used in tissues needing both Rib 5-P & NADPH
  - ATP is plentiful
- Used in tissues requiring more NADPH than Rib 5-P
  - such as the liver and adipose tissue

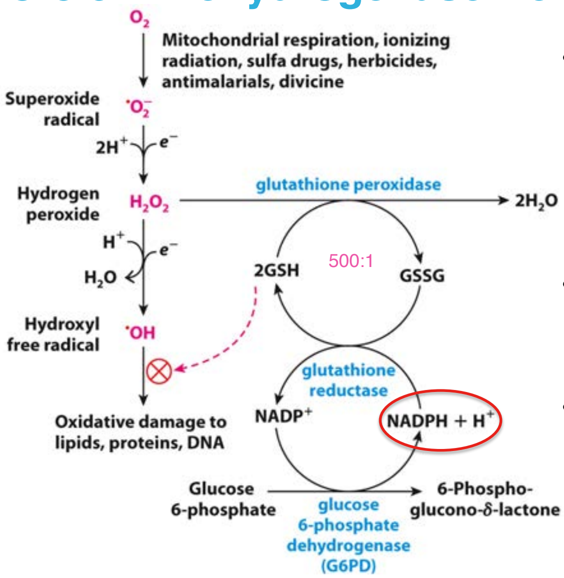




- Used in tissues requiring more Rib 5-P than NADPH
  - such as the lymphocytes and fast growing tissues/cancer cells

Pentose Phosphate Pathway

Glc 6-P Dehydrogenase Deficiency*



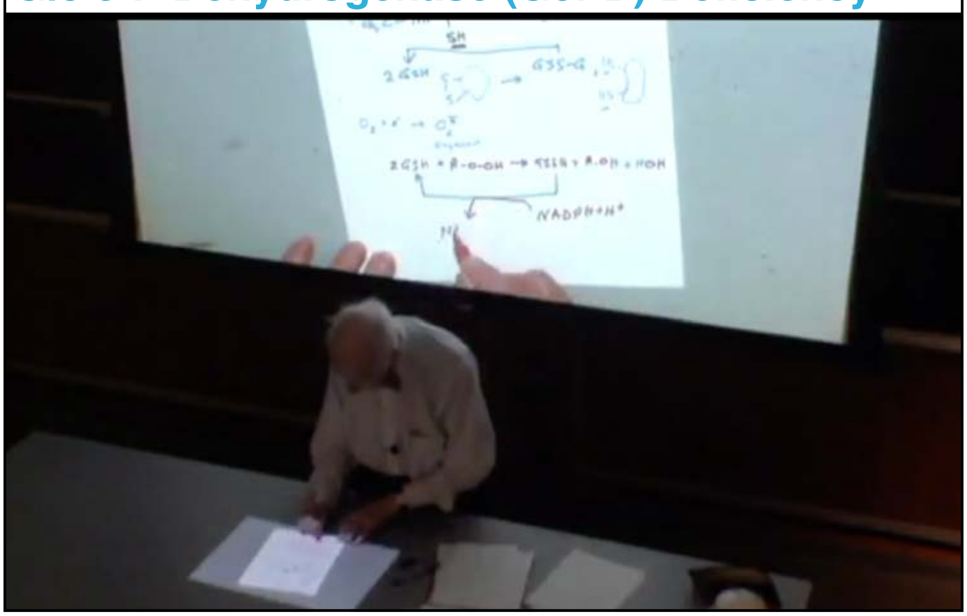
- Can be fatal in cases of high oxidative stress. Hemolytic anemia
  - certain drugs, herbicides, and some foods (fava beans)
- Resistance to malaria due to high oxidative stress in red blood cells
- X-linked heterozygous advantage

Essential for red-blood cells

*Total lack of G6PDH is lethal

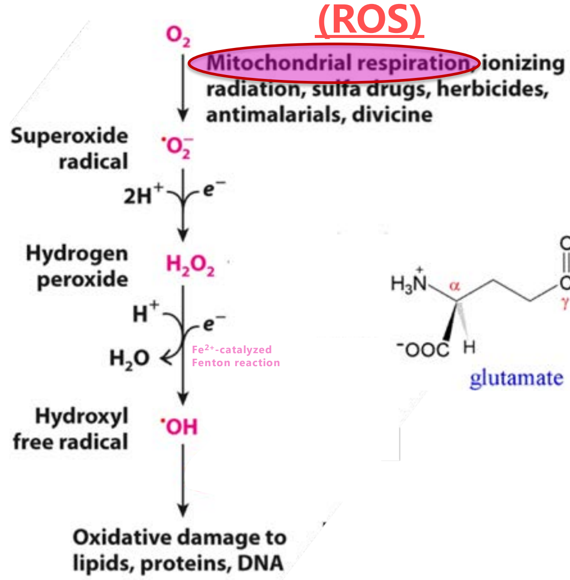
Pentose Phosphate Pathway

Glc 6-P Dehydrogenase (G6PD) Deficiency*

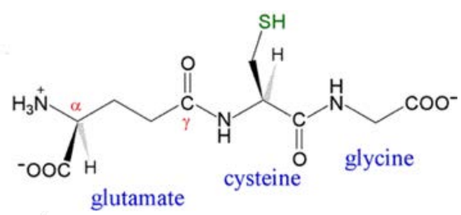


Pentose Phosphate Pathway

Reactive Oxygen Species (ROS)

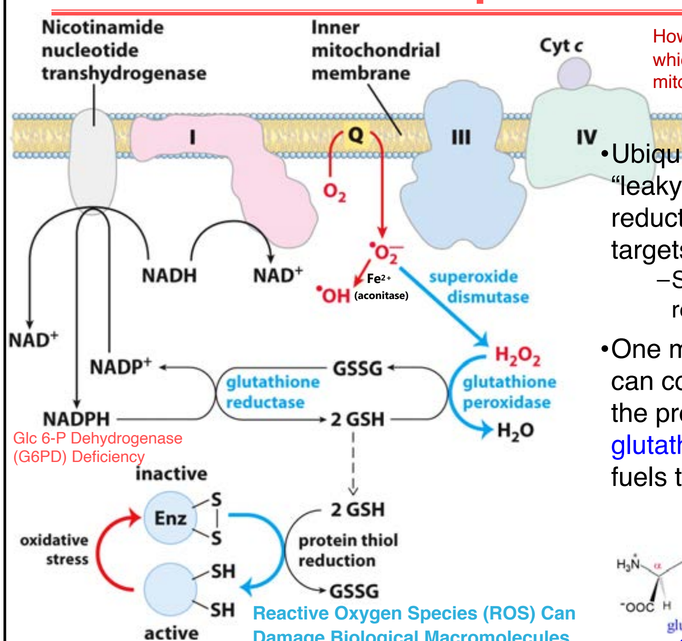


Glutathione (GSH)



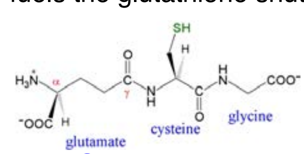
γECG

Pentose Phosphate Pathway



How do we get **NADPH** from PPP, which is made in the cytosol, into mitochondria?

- Ubiquinone is naturally “leaky” and facilitates partial reduction of non-Complex III targets.
  - Single electron transfers result in free radicals.
- One method by which the cell can correct free-radicals is the production of reduced glutathione (GSH), which fuels the glutathione shuttle



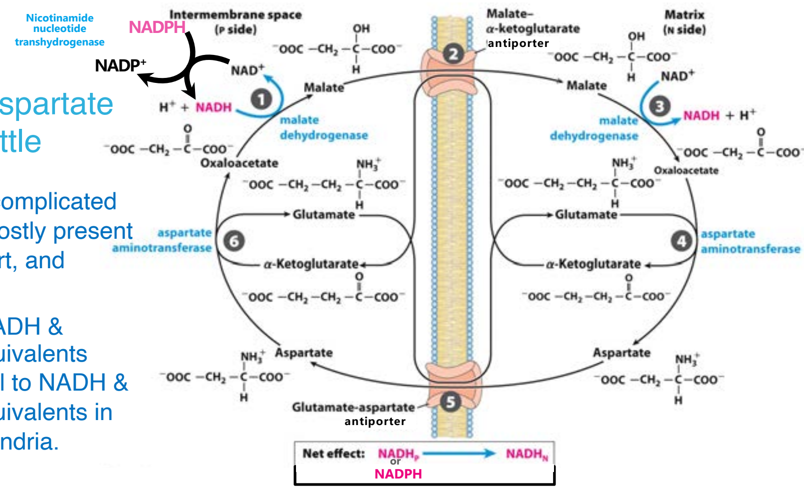
Glutathione

Pentose Phosphate Pathway

Converting Cytosolic Electron Carriers (NADPH from PPP & NADH from glycolysis) to the Mitochondria

Malate-Aspartate Shuttle

- This more complicated shuttle is mostly present in liver, heart, and kidney.
- It moves NADH & NADPH equivalents from cytosol to NADH & NADPH equivalents in the mitochondria.



Regulation of Carbohydrate Metabolism

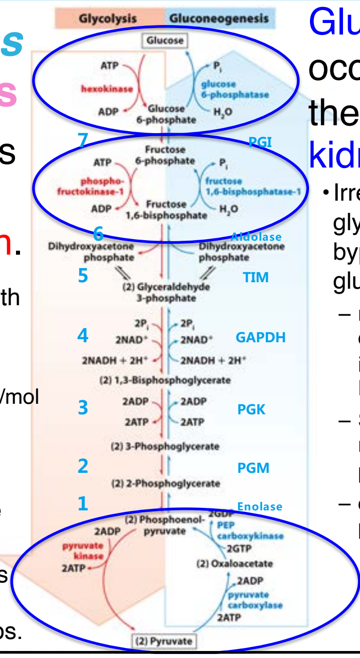
Catabolism ***vs.*** **Anabolism**

Gluconeogenesis

Glycolysis *versus* Gluconeogenesis

Glycolysis occurs mainly in the muscle and brain.

- Opposing pathways that are both thermodynamically favorable:
- Glycolysis: $\Delta G^{\circ\prime} = -35$ kcal/mol
- Gluconeogenesis: $\Delta G^{\circ\prime} = -9$ kcal/mol
  - operate in opposite direction
    - end product of one is the starting compound of the other
- Seven Reversible reactions are used by both pathways.
- Three "glycolysis-specific" steps are reversed with Four "gluconeogenesis-specific" steps.



Gluconeogenesis occurs mainly in the liver and kidney cortex.

- Irreversible reactions of glycolysis must be bypassed in gluconeogenesis.
  - no ATP generated during gluconeogenesis; instead 6 ATPs and 2 NADH needed per Glc.
  - Some different enzymes results in the different pathways
  - differentially regulated to prevent a futile cycle

Regulation of Carbohydrate Metabolism

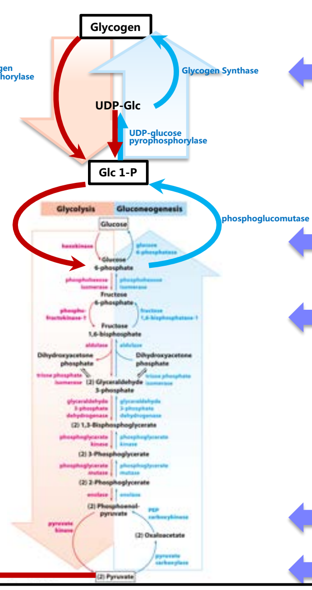
Gene controlled

Glycogenolysis ↓
versus
Glycogen Synthesis ↑ Glycogen Phosphorylase

Glycolysis ↓
versus
Gluconeogenesis ↑

- Regulated enzymes often correspond to points in the pathways that have the same substrate and product, but a different enzyme.
- Also where there are junctions.

- Can you name those enzymes?

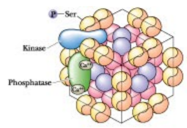


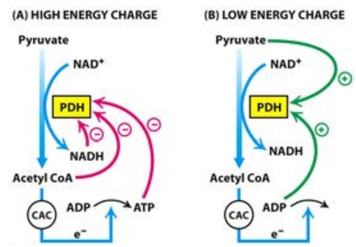
Acetyl-CoA

Catabolism	Anabolism
Phosphorylase	Glycogen Synthase
Hexokinase	Glucose 6-phosphatase
Phosphofructo-kinase-1	Fructose 1,6-bisphosphatase -1
Pyruvate Kinase	– PEPCK – Pyruvate carboxylase
Pyruvate Dehydrogenase Complex	

Regulation of Carbohydrate Metabolism

Regulation of Pyruvate Dehydrogenase Complex





- Allosteric regulation by energy charge and substrate/product
  - –ADP & pyruvate activates
  - –ATP/NADH & acetyl-CoA inhibit
- Regulated by reversible phosphorylation of E1
  - –phosphorylation: inactive
  - –dephosphorylation: active
- PDH kinase and PDH phosphatase are part of mammalian PDH complex.
  - –Kinase is activated by ATP.
    - high ATP → phosphorylated PDH → less acetyl-CoA made
    - low ATP → kinase is less active and phosphoprotein phosphatase removes phosphate from PDH → more acetyl-CoA made